UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,487	02/10/2004	Denise L. Faustman	00786/457003	1044

21559 7590 09/13/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/13/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/775,487	FAUSTMAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2007 and 02 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-82* is/are pending in the application.

4a) Of the above claim(s) *78,81 and 82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76,77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-2-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the specification and Remarks filed June 20, 2007 are acknowledged.

   Claims 76-82 are pending.

   Claims 78, 81 and 82 have been withdrawn from consideration.

   Claims 76, 77, 79 and 80 are under examination as they read on a method for treating an autoimmune disease with a substance that stimulates NFKB signaling, wherein the elected species of autoimmune disease is "diabetes".

2. Applicant's amendment to the specification and Remarks filed June 20, 2007 are responsive to the Office Action mailed December 15, 2006.

   The previous objection to the oath/declaration has been withdrawn in view of applicant's submission of a Supplemental Application Data Sheet.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, written description, has been withdrawn in view of applicant's argument.

   The previous rejection under 35 U.S.C. § 102(b) have been withdrawn upon further consideration and in view of applicant's argument.

   The previous rejection under 35 U.S.C. § 102(e) has been withdrawn in view of applicant's argument.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, enablement is maintained for the reasons of record put forth in the Office Action of December 15, 2006 and for the reasons put forth below.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 76, 77, 79 and 80 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating pre-clinical type I diabetes in non-obese diabetic mice does not reasonably provide enablement for treating overt type I diabetes in any autoimmune disease in any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant's arguments in conjunction with the declaration under 35 U.S.C. § 1.132 of Dr. Denise Faustman have been considered but have not been found convincing, essentially for the reasons of record.

The data disclosed in the instant specification referred to in applicant's arugment is summarized below:

1. Spleen cells were obtained from mice bred to be non-obese and diabetic (NOD) and wild type mice, stimulated with TNF-α and then protein extracts were prepared and characterized. This showed that NOD spleen cells are defective in producing the "active" signaling form of NFKB whereas spleen cells obtained from wild type mice are not (see instant specification page 113, line 16, through page 116, line 2 and Figures 8A-8D);

2. Spleen cells were obtained from NOD and wild type mice, stimulated with TNF-α, and then protein extracts were prepared and characterized. This showed the reason NOD spleen cells are defective in producing the "active" signaling form of NFKB is because a defect in the NOD mouse proteosome (proteosomal cleavage is required for the "active" signaling form of NFKB to be released from the IKB inhibitor upon TNF-α signaling)(see instant specification page 124, lines 20-22); and

3. Spleen cells were obtained from NOD and wild type mice, stimulated with TNF-α, and then cell viability was measured. The NOD spleen cells died and underwent apoptosis while the wild type cells did not (see instant specification page 126, line 5 through page 127, line 6 and Figures 13A-13D).

Applicant asserts that "NOD mice [are] an accepted animal model for treatment of type 1 (autoimmune) diabetes mellitus, Sjogren's syndrome, and lupus in humans",

and based on this assertion and the data given in points 1-3 above concludes:

"applicant recognized that defects in NFkB signaling was a common denominator across several autoimmune diseases..."

Applicant then directs the Examiner to the Declaration of co-inventor Faustman as further evidence that the specification teaches the skilled artisan how to make and use the full scope of the claimed invention without "undue experimentation," i.e., that is enabling.

Before addressing the Faustman Declaration, a few things concerning applicant's argument presented above should be addressed.

The disclosure of a series of experiments in which spleen cells were isolated from a particular mouse strain (i.e., the NOD mouse), which has a particular set of genetic defects (e.g., defective proteosome activity leading to defective NFKB signaling) and manipulated in vitro to show that these spleen cells can be killed by TNF-α does not provide sufficient guidance or direction for the skilled artisan to treat any autoimmune disease of diverse etiology, related only in the broadest of terms, i.e., they have an "HLA class II-linkage," (see the instant specification at page 37, 4th-5th paragraphs) in any mammal, including humans who are well known by the skilled artisan to exhibit heterogeneous multi-genic disease factors.

Moreover, while it is fair to say that a mouse predisposed to type I diabetes (a non-obese *diabetic* mouse (NOD)) can be induced to have *lupus* like symptoms, this does not mean the data disclosed in the instant specification is necessarily representative of spleen cells one would find in a NOD mouse induced to have *lupus* as implied by applicant's argument. This is because the bacteria Bacillus Calmette-Guerin (BCG) must be administered to a NOD mouse to induce *lupus* (see, for example, Baxter et al. (Immunology. 1994 Oct;83(2):227-31, in particular, page 230, right column)), and the experiments disclosed in the instant specification do not concern spleen cells obtained from NOD mice administered BCG. Moreover, it should be noted that NOD mice administered BCG, while modeling lupus, are in fact protected from developing type I diabetes by a mechanism dependent on splenic macrophage (see, ibid, in particular, Discussion on pages 229-230, in particular, page 229, right column). So the experimental data disclosed in the instant specification is not necessarily generalizable to a NOD mouse in which lupus has been induced as suggested by applicant's argument.

Furthermore, as stated in the previous Office Action, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the

method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

With respect to the Faustman declaration in particular, there are essentially three substantive parts.

In the Introduction (sections 1-3) Dr. Faustman's credentials and the issue at hand are presented. In Part I (sections 5 and 8) Dr. Faustman reviews the data of the specification concerning the effect of administering TNF-α to spleen cells isolated from a NOD mouse and presents additional data using a NOD mouse. In Part II (sections 6, 7 and 9), Dr. Faustman presents data in support of applicant's assertion that administration of TNF-α could be used to treat disparate autoimmune diseases. Finally in Part III (section 4) Dr. Faustman gives her opinion as to what she and her coinventor have discovered.

An analysis of each substantive part is presented below.

Part I: Sections 5 and 8

In section 5, Dr. Faustman reviews the data disclosed in the instant specification that spleen cells isolated from NOD and wild type mice are defective in NFKB signaling in response to TNF-α stimulation and therefore undergo apoptosis when exposed to TNF-α.

With respect to section 5, as essentially stated in the prior Office Action and above, the instant specification discloses a series of experiments in which spleen cells were isolated from a particular mouse strain with a genetically determined predisposition to type I diabetes, i.e., the NOD mouse strain and exposed to TNF-α in vitro. The NOD mouse has a particular set of genetic defects, e.g., defective proteosome activity leading to defective NFKB signaling. Exposure of isolated NOD mouse spleen cells in vitro to TNF-α shows they can be killed by TNF-α.

While the data in the instant specification suggests at least one mechanism that may explain the observations in the prior art that TNF-α can be used to inhibit the development of overt type I diabetes in NOD mice (see, for example, Jacob et al., Proc Natl Acad Sci U S A. 1990 Feb;87(3):968-72, cited in applicant's IDS of July 2, 2007 and described in more detail below), it still does not provide sufficient direction or guidance for the skilled artisan to practice the claimed method in vivo in a human.

In section 8, Dr. Faustman presents new data purporting to show that transfer of "autoreactive T cells" from an "an autoimmune mouse" (presumably a NOD mouse) treated with BCG "a well known inducer of endogenous TNF" to a normal mouse is far less potent at inducing diabetes in said normal mouse than adoptively transferred "autoreactive T cells" not treated with BCG (see Exhibit C).

With respect to section 8, there is either insufficient experimental details and/or insufficient data provided to understand the true significance of the statements made in this section or the new data of Exhibit C.

For example, Section 8 indicates that "I have further confirmed that other substances that induce endogenous TNF-α expression promote autoreactive immune cell death. For example, BCG, a well known inducer of endogenous TNF, when administered to autoreactive animals with type I diabetes, lupus, or Sjogren's syndrome, successfully delays onset of disease in these animals."

However, no data appears to have been presented in support of this conclusion either in the instant specification or in Dr. Faustman's declaration so it is difficult to evaluate this statement or understand how it fits into the context of the disclosure of the instant specification.

With regard to Exhibit C in particular, it shows that "autoreactive T cells" obtained from an "an autoimmune mouse" (presumably a NOD mouse) treated with BCG "a well known inducer of endogenous TNF" and then transferred to a normal mouse are far less potent at inducing diabetes in said normal mouse than adoptively transferred "autoreactive T cells" not treated with BCG. However, it is nowhere made clear what the source of the "autoreactive T cells" is, i.e., are they spleen cells from a NOD mouse isolated in the same way as the spleen cells used in the experiments disclosed in the instant specification, or are they some other autoreactive T cell or subset of spleen cells?

Furthermore, Dr. Faustman's conclusion that "[t]his data demonstrates selective autoreactive immune cell elimination by a TNF-α inducer substance in the same manner as that observed using TNF-α and TNF-α agonist antibodies," is also vague and unclear.

Does "selective autoreactive immune cell elimination... in the same manner as that observed using TNF-α," mean that the "autoreactive T cells" from "an autoimmune mouse" were treated with BCG, grown in culture long enough for cell death to occur as in Figure 10 of the instant specification, and then transferred to wt recipient? Or does "selective autoreactive immune cell elimination... in the same manner as that observed using TNF-α," mean, for example, that the "autoreactive T cells" from "an autoimmune mouse" were treated with BCG, and then immediately transferred to the wt recipient? In any case, there are multiple potential explanations for the observed effect of BCG treated cells that are not made clear by the declaration, and the declaration does not provide sufficient detail to simply conclude that treating cells with BCG is the same as treating them with TNF-α. For example, as taught by McInerney (Diabetes. 1991 Jun;40(6):715-25), BCG treatment of spleen cells (wherein BCG is in the form of complete freund's adjuvant of CFA), "...prevents the development of diabetes, and concomitantly, insulates while stimulating the generation of spleenic suppressor cells that are capable of suppressing diabetogenic T-lymphocyte function in vivo and in vitro." (see, in particular, Abstract on page 715).

However, the data shown in Exhibity C was obtained, the details need to be made clear in order to properly understand the meaning of Section 8 and how it fits in with the disclosure of the instant specification.

Thus, even when considered together, the data disclosed in the instant specification and the new data provided in Exhibit C are insufficient to demonstrate that the skilled artisan could have used TNF-α, or a TNF-α agonist, to treat type I diabetes, or any other autoimmune disease, in a human without undue experimentation. These experiments do not provide sufficient guidance or direction for the skilled artisan to treat any autoimmune disease of diverse etiology, related only in the broadest of terms, i.e., they have an "HLA class II-linkage," (see the instant specification at page 37, 4th-5th paragraphs) in any mammal, including humans who are well known by the skilled artisan to exhibit heterogeneous multi-genic disease factors.

Part II: Sections 6, 7 and 9

With respect to section 6 in particular, referring to Exhibit A, Dr. Faustman describes how in culture, only "*the specific subpopulation of autoreactive T cells* from patients diagnosed with the indicated autoimmune diseases die when exposed to a TNF agonist." This statement is too vague to be properly evaluated and the data presented in Exhibit A does not further clarify. For example, what exactly is meant by the phrase ""*the specific subpopulation of autoreactive T cells"?* Are these peripheral blood T cells, spleenic T cells, T cell lines established from autoimmune patients, all $CD4^+$ T cells or just Th1 T-cells? Are these cells obtained from the general population of autoimmune patients or some selected subgroup of patients? Also what does "autoimmune samples studied" in Exhibit A refer to, the total number of samples studied, a subset of which were killed by TNF-α, or that, for example, in >8 samples from scleroderma all T cells in this sample were killed by TNF-α? If the former, what percentage of the total autoreaction T cells in the sample were killed by TNF-α? Do the T cells killed by TNF-α actually have a defect in NFkb signaling?

With respect to section 7 in particular, referring to Exhibit B, Dr. Faustman presents new data and states that it confirms that TNF-α agonists other than TNF-α promote "autoreactive immune cell death," as shown for TNF-α agonistic antibodies in Exhibit B which is "an average of data from experiments performed using cells from patients" having diabetes, lupus, multiple sclerosis, psoriasis, Crohn's, and rheumatoid arthritis. However, the skilled artisan would be hesitant to draw any conclusion about treating a large number of disease of distinct etiologies based on an average value of these diseases. Moreover, the same considerations about the patients sampled and the types of T cells involved as in Exhibit A are applicable here. Furthermore, even the most basic experimental conditions are not established by the Declaration or Exhibit such as was this an in vitro experiment, and if so what cells other than T cells were contained in these samples?

Thus, as in Part I of the Declaration, there is either insufficient details and/or insufficient data provided to understand the true significance of the statements made in this part of the declaration.

With respect to section 9, Dr. Faustman presents a large number of new references purporting to show that "while anti-TNF therapies certainly can remove inflammation and thus improve the symptoms of autoimmunity, my data and other pre- and post-filing date publications suggest that anti-TNF therapy could exacerbate or elicit new autoimmune disease in some patients. Indeed, neutralization of TNF by drug therapy with anti-TNF has been shown to induce, in some cases, new or exacerbated autoimmunity (see Exhibit D)."

Dr. Faustman concludes: "In combination with the new onset demyelization, side effects of anti-TNFα therapy in both rheumatoid arthritis and Crohn's disease, the data are consistent with some autoimmune patients not benefiting from the removal of TNF (see, e.g., Enayati and Papdakis..."

The declaration cites numerous references purporting to show that there are cases in which anti-TNF-α treatment appears to induce an autoimmune disease (these disease are displayed graphically in Exhibit D). However, the declaration does not give any analysis of the disclosure of these references other than to generically categorize them by relevant disease. For example, of the total autoimmune patients treated with TNF-α antagonists, how many end up with a second autoimmune disease, how does this rate of occurrence compare to the rate of occurrence in autoimmune patients not treated with TNF-α antagonists, and are the autoimmune cells of these patients sensitive to killing by agents that stimulate NFKB, such as TNF-α? Also, the "autoantibodies" column seems to be out of frame and furthermore, in the absence of any discussion whatsoever, it is not clear how the presence of the particular anti-nuclear and anti-dsDNA autoantibodies relates to the purported presence of autoreactive T cells that cannot signal through the NFKB pathway and that would otherwise be killed by TNF-α?

Moreover, it should be pointed out that the scope of the instant claims are not limited only to those patients in which antagonizing TNF-α exacerbates disease. Rather the instant claims encompass in their breadth a method of treating any patient having any autoimmune disease. Even if assuming, arguendo, that all patients with autoimmune disease have at least some autoreactive T cells that can be killed with an agent that stimulates NFKB signaling, such as TNF-α, applicant still has not addressed how this method of treatment would be effective in view of the substantial art teachings pro-inflammatory effects of TNF-α on other cells involved in autoimmune disease.

For example, as put forth in the Office Action of December 15, 2006, with respect to diabetes in particular, Corbett et al. (Proc Natl Acad Sci U S A. 1993 Mar 1;90(5):1731-5) teaches that in human cells TNF-α potentiates the IL-1 + IFN-γ induced production of nitric oxide, a molecule which participates in the beta-cell dysfunction associated with insulin-dependent diabetes mellitus (see entire document, in particular Abstract and pages 1731-1732). Likewise, Altomonte et al. (Clin Rheumatol. 1992 Jun;11(2):202-5) also cited in the previous Office Action, teaches that TNF-α can induce the production of IL-1b, and that both molecules can act locally to induce bone and cartilage resorption, synoviocyte proliferation and the production of prostaglandins and proteases that amplify the destructive process in the joint (see, for example, Introduction, in particular page 202) – certainly not something you would want to do in a rheumatoid arthritis patient or a lupus patient who often has overlapping symptoms with the RA patient. Furthermore, as taught by Feldman et al. (Transplant Proc. 1998 Dec;30(8):4126-7, cited on applicant's IDS of July 2, 2007), TNF-α is involved in the expression of various adhesion molecules responsible for recruiting leucocytes to inflammatory sites (see, in particular, page 4126, right column, 1st paragraph).

Part III: Section 4

In Section 4, Dr. Faustman states the following conclusions: "My co-inventor and I discovered that genetic defects altering NFkb activity are a common denominator across several autoimmune diseases, including the following: Type I diabetes, lupus, Crohn's disease, Sjogren's syndrome, autoimmune glandular diseases [autoimmune polyendocrinopathy syndrome (APS)-I or autoimmune polyendorinopathy candidasis ectodermal dystrophy], hypothyroidism, multiple sclerosis, psoriasis, and scleroderma. NF-kb dysregulation has been found not only in humans but in at least two animal models of autoimmune disease. Although the particular modulator of NF-kb activity varies by disease, the diseases remarkably overlap by almost uniformly hampering NF-kb formation or functional activity in ways that are particular to the immune cell type and autoimmune disease. Moreover, we discovered that one result of the genetic defects in NF-kb activity is that the autoreactive immune cells responsible for development of autoimmune diseases are sensitive to exposure to TNF-α, which induces cell death in these cells. Thus, our data confirm that multiple, disparate autoimmune diseases can be treated by administering a TNF-α agonist, such as a TNF-α or other TNF-α inducing substance, which promotes cell death in the autoreactive immune cells responsible for, or responsible for exacerbating, the disease condition."

However the "conclusions" given above are either not supported by the evidence presented in the declaration for the reasons given above (e.g., "our data confirm that multiple, disparate autoimmune diseases can be treated by administering a TNF-α agonist, such as a TNF-α or other TNF-α inducing substance") or apparently not even commented upon in the instant declaration (e.g., "NF-kb dysregulation has been found...in at least two animal models of autoimmune disease").

It is also noted that applicants IDS submitted July 2, 2007 raised an additional issue pertaining to the breadth of the instant claims.

In particular, the instant claims recite "a method of treating a mammal having an autoimmune disease". The phrase "a method of treating a mammal having an autoimmune disease,' given its broadest reasonable interpretation consistent with the instant specification, reads on treating those patients with symptoms of overt, frank clinically diagnosable disease, as well as those patients who have more subtle, predisease symptoms which precede clinical disease. For example, in the case of type I diabetes there is a prediabetic stage where autoantibodies and decreased insulin response to glucose are evident before clinical symptoms.

Jacob et al. (Proc Natl Acad Sci U S A. 1990 Feb;87(3):968-72, cited in applicant's IDS of July 2, 2007) teach that TNF-α is effective at preventing diabetes in non-obese diabetic mice. According to this reference, disease was prevented in NOD mice treated with TNF-α starting at the age of 8-12 weeks dependent on the particular experiment (see ibid, in particular, Abstract, Introduction and Materials and Methods on page 968). As evidenced by Anderson et al. (Annu Rev Immunol. 2005;23:447-85), frank, overt symptoms of clinical diabetes do not occur in NOD mice until at least 12-14 weeks (see, in particular, page 448, 2nd paragraph). Thus, while the prior art establishes that type I diabetes can be inhibited in NOD mice when the mice are treated in the prediabetic phase, it does not teach treating overt diabetes with a TNF-α agonist. Moreover, even if it did, given the unpredictability in the art of treating autoimmune disease in humans, including type I diabetes, by agonizing TNF-α as described above, it is far from clear that administration of TNF-α would have anything other than a detrimental effect on either prediabetes or overt diabetes in a human.

Thus, when Applicant's arguments and objective evidence are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remains non-enabled in view of the nature of the invention and the state and unpredictability of the art. See M.P.E.P. § 716.01(d).

Applicant's submission of the IDS of July 7, 2007 prompted the New Grounds of Rejection set forth below.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 76, 77 and 80 are rejected under 35 U.S.C. 102(b) as anticipated by Jacob et al. (Proc Natl Acad Sci U S A. 1990 Feb;87(3):968-72, cited in applicant's IDS of July 2, 2007) in view of Anderson et al. (Annu Rev Immunol. 2005;23:447-85).

The instant claims recite "a method of treating a mammal having an autoimmune disease". The phrase "a method of treating a mammal having an autoimmune disease,' given its broadest reasonable interpretation consistent with the instant specification, reads on treating those patients with symptoms of overt, frank clinically diagnosable disease, as well as those patients who have more subtle, predisease symptoms which usually precede the development of clinical disease. For example, in the case of type I diabetes there is a prediabetic stage where autoantibodies and decreased insulin response to glucose are evident before clinical symptoms.

Jacob teaches that TNF-α is effective at preventing diabetes in non-obese diabetic mice. According to Jacob, disease was prevented in NOD mice treated with TNF-α starting at the age of 8-12 weeks dependent on the particular experiment (see entire document, in particular, Abstract, Introduction and Materials and Methods on page 968). Given that these animals are highly predisposed to type I diabetes as evidenced by the controls presented in Jacob (see, for example, Tables 1 and 2, PBS treated NOD mice), and further given that the treated animals were given TNF-α just before the time that overt symptoms first begin to appear, i.e., at 12-14 weeks as evidenced by Anderson (see, in particular, page 448, 2nd paragraph) and continuing for weeks or months thereafter until the control mice had various signs of prediabetic state (see Jacob Table 2) or overt disease (see Jacob table 1), Jacob is inherently teaching the treatment of prediabetic mice with TNF-α.

Thus, Jacob anticipates the instant claims.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 76, 77, 79 and 80 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 6,660,487.

9. Additionally, claims 76, 77, 79 and 80 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-30, 65-73 and 91-108 of copending USSN 10/851,983.

   Applicant has indicated that when the pending claims are found to be allowable other than for the double patenting rejections, applicant will address the double patenting rejections and/or file a terminal disclaimer.

10. No claim is allowed.

11. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on July 2, 2007 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

    A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m..
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
August 28, 2007

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

08/31/07